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Validation of an animal model of right ventricular dysfunction and right bundle branch block to create close physiology to postoperative tetralogy of Fallot

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ABSTRACT

Background: In the past 5 years a few number of studies and case reports have come out focusing on biventricular (BiV) stimulation for treatment of congenital heart disease related ventricular dysfunction. The few available studies include a diverse group of pathophysiological entities ranging from a previously repaired tetralogy of Fallot (TOF) to a functional single ventricle anatomy. Patient's status is too heterogeneous to build important prospective study. To well understand the implication of prolonged electromechanical dyssynchrony we performed a chronic animal model that mimics essential parameters of postoperative TOF.

Methods: Significant pulmonary regurgitation, mild stenosis, as well as right ventricular outflow tract (RVOT) scars were induced in 15 piglets to mimic repaired TOF. 4 months after hemodynamics and dyssynchrony parameters were compared with a control group and with a population of symptomatic adult with repaired TOF.

Results: Comparing the animal model with the animal control group on echocardiography, RV dilatation, RV and LV dysfunction, broad QRS complex and dyssynchrony were observed on the animal model piglets. Moreover, epicardial electrical mapping showed activation consistent with a right bundle branch block. The animal models displayed the same pathophysiological parameters as the post TOF repair patients in terms of QRS duration, pulmonary regurgitation biventricular dysfunction and dyssynchrony.

Conclusion: This chronic swine model mimics electromechanical ventricular activation delay, RV and LV dysfunction, as in adult population of repair TOF. It does appear to be a very useful and interesting model to study the implication of dyssynchrony and the interest of resynchronization therapy in TOF failing ventricle.

1. Introduction

Isolated right heart failure is a relatively common disorder with multiple causes such as congenital heart disease, pulmonary arterial hypertension, right ventricular infarction, and acquired right heart valvular disease. The pathophysiology and clinical course of these diseases are often poorly understood. As a result of major improvements in surgical technique, postoperative care and medical management in recent years the population of adults with repaired tetralogy of Fallot (TOF) and other congenital heart diseases is increasing. The growth of this population is linear [1] and the mortality rate, at least in the early adult years, is relatively low [2]. This nascent demographic phenomenon is creating major issues concerning the optimal management of adults with congenital heart disease [3]. The surgical repair of TOF is highly successful, though may be later complicated by right ventricular dysfunction due to volume and pressure overload and by late sudden death. The incompletely understood mechanisms of these delayed adverse developments may be partially due to the surgically-induced permanent right bundle branch block (BBB) and ventricular dyssynchrony [4–9]. Therapeutic options remain limited. Implantation of a cardiac resynchronization therapy defibrillator has recently been proposed in TOF patients to decrease sudden death and to improve hemodynamic status. However, studies of the safety and efficacy of cardiac resynchronization in patients with congenital heart disease and RV dysfunction are limited to case reports, retrospective analyses of heterogeneous

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populations and small crossover trials conducted in the immediate postoperative period [10–15]. To identify risk factors leading to sudden death in TOF patients [16–18] and to define mechanisms involved in hemodynamic improvement induced by cardiac resynchronization [8,19], we aimed to develop a viable and reproducible swine model recapitulating the findings of right heart failure and right bundle branch block observed after prior surgical repair of TOF.

The aims of the present study were to 1) develop a reliable and reproducible long-term swine model of RV dysfunction and RV dyssynchrony and 2) to compare echocardiographic measurements of right ventricular dysfunction, dilatation and dyssynchrony in this animal model and adult patients with previously repaired TOF.

2. Methods

2.1. Studies in an animal model of repaired TOF

Our experimental protocols were in compliance with the *Guiding Principles in the Use and Care of Animals* published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996).

2.1.1. Construction of the swine model

The experimental study included 15 newborn piglets weighing <8 kg. Animals were sedated with a 20-mg/kg, intramuscular injection of ketamine hydrochloride, and anesthetized with 10 mg/kg of sodium pentobarbital before endotracheal intubation. Anesthesia was continued with ketamine 500-mg/h, and prophylactic intravenous antimicrobials were administered. Peripheral oxygen saturation, heart rate, and blood pressure were monitored continuously. All surgical study animals received a muscle-sparing left thoracotomy between the fourth or fifth interspace.

Surgical intervention was then designed to cause (Fig. 1)

1) RV volume overload from valvular regurgitation effected by means of placement of a vascular clamp longitudinally across the pulmonary valve annulus without obstruction of the RV outflow tract. A 2-cm incision was made longitudinally across the pulmonary annulus, and 2 pulmonary valve leaflets were excised. A 2-cm-long elliptically shaped polytetrafluorethylene patch was sewn in place with 6-0 nonabsorbable monofilament sutures across the annulus to ensure complete disruption of valve integrity.
2) RV pressure overload, via a pulmonary artery band placed 1 cm distal to the valve annulus. After dissection, a loosely tied tape was passed around the artery and secured for a final diameter of approximately 2 cm.
3) RV outflow tract scar, a 1-cm full-thickness incision was made longitudinally over the infundibulum up to but not including the valve annulus and then repaired with the placement of a 1-cm-long elliptically shaped polytetrafluorethylene patch to ensure scar formation.

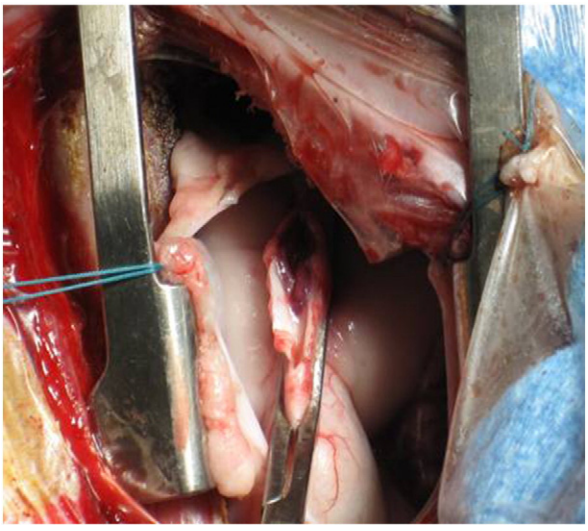

Fig. 1. Surgery procedure: Sparing left thoracotomy between the fourth or fifth interspace. Vascular clamp is longitudinally placed across the pulmonary valve annulus without obstruction of the RV outflow tract, longitudinal incision on 2 cm and excision of 2 pulmonary valve leaflets. Closure using an elliptically shaped polytetrafluorethylene patch sewn with nonabsorbable monofilament sutures.

After completion of the procedure, animals were extubated and received supplemental oxygen and analgesia as needed before their transfer to a long-term postoperative care facility.

2.1.2. Study of the animal model

The index operation was performed in 15 animals, of whom 1 died in the immediate, and 2 in the late postoperative period. After 4 months of postoperative recovery, the animals were sedated, intubated and anesthetized in the catheterization laboratory, as described earlier. A 7F catheter was introduced into the internal jugular vein for infusion of pharmaceuticals and fluids. The heart was exposed via median sternotomy and lateral thoracotomy and suspended in a pericardial cradle. After stabilization for 20 min, baseline LV pressure, aortic flow and the surface electrocardiogram were recorded. The signals were digitized at 200 Hz and stored on disk for off-line analysis. Echocardiographic measurements were then performed in the first 7 animals alive. The same experimental protocol was carried out, and the same measurements were made for comparison in a control group of 7 age-matched, previously non-operated animals.

2.1.3. Electroanatomic mapping in the animal model

Five animals were similarly operated 4 months after the index procedure and underwent epicardial electroanatomic mapping with Carto™ (Biosense Webster, Diamond Bar, CA), as previously described [20]. The torso of the animal was covered by 3 magnetic fields of different frequencies. A location reference was fixed on the back of the pig while a mapping catheter navigated on the epicardium of the animal. The magnetic sensor equipped in the tip of the catheter and the location reference compared the intensities of the 3 magnetic fields ensuring that the location of the catheter could be accurately determined. Color-coded, 3-dimensional maps of epicardial activation were constructed.

2.2. Studies in adult patients with TOF

A total of 42 consecutive patients aged >18 years with a history of surgically repaired TOF, in sinus rhythm with electrocardiographic signs of the right bundle branch block (QRS duration >120 ms) were prospectively included for an echocardiographic evaluation. Exclusion criteria were inadequate transthoracic window for echocardiographic examination and the presence of a pacing device. Electrocardiographic and ultrasound data from these patients were compared with those obtained from 30 control subjects, matched for age and free of any history of acquired or congenital heart disease. The median age was 29 ± 6 years in patients vs. 26 ± 7 years in controls (P = ns). The median age at TOF repair was 5.4 ± 4.7 years. Twenty-four patients were in NYHA functional class I, 15 in class II, and 3 in class III, despite optimal medical therapy. The mean QRS duration in the TOF group was 154 ± 21 ms with an RBBB aspect vs. 88 ± 8 ms in the control group ($p<0.0001$).

2.3. Echocardiographic study in the animal model and in patients

The animals with the model of repaired TOF, the control animals, the patients with TOF and the control patients underwent the same echocardiographic protocol. Transthoracic echocardiography was performed with a Vivid 7 digital ultrasound system (GE/VingMed, Horten, Norway) (Fig. 2). Echocardiographic cine-loops of 3 cardiac cycles were analyzed off-line to confirm the presence of pulmonic valve stenosis. By using continuous Doppler waveforms, the pulmonary regurgitation pressure half-time (PHT) was measured. The PHT was measured from the initial linear downslope of the pulmonary regurgitation waveform. A PHT value of <100 ms determined a severe pulmonary regurgitation. Tissue Doppler imaging of segmental wall motion was used to quantify intra-LV and intra-RV dyssynchrony as previously described. Briefly, intra-LV dyssynchrony was defined as the difference between the shortest and longest of 4 basal LV electromechanical delays (lateral, septal, anterior and inferior). Intra-RV dyssynchrony was defined as the difference between electromechanical delay of septum and RV free wall. The systolic RV function was assessed by measuring of peak systolic TDI velocity ~1 cm towards the apex from the lateral tricuspid valve annulus in the apical four-chamber view.

2.4. Statistical analysis

Data were expressed as mean value ± SD. Comparisons between the groups were made using Student's *t*-test. Control subjects and animals were included in the study to estimate the range of ventricular dyssynchrony, contractility and dimensions in the population with normal cardiac function and no history of cardiomyopathy. For all analyses, a *P*-value less than 0.05 was considered statistically significant.

3. Results

3.1. Animal experiments

3.1.1. Characteristics of the animal model

Compared to the control group, the operated animals developed prominent pulmonic stenosis and regurgitation, RV pressure and